REMARKS

Claims 1-42, of which claims 1, 10, and 21 are currently amended and claims 41-42 are new, are pending and appear in this application for the Examiner's review and consideration. Claims 1, 10, and 21 are amended for clarity. New claims 41-42 are added as being directed to embodiments of the invention. Support for the amendments are found in the original claims and throughout the specification, for example, in the Physiological Examples. As no new matter is introduced, entry of the amendments at this time is warranted. In the following remarks, citations of the specification are made with reference to paragraph numbers of the published application, U.S. Publication No. US 2005/0032881.

Applicants acknowledge with appreciation the Examiner's indication of allowability of claims 1-20 and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, of claims 1, 2, 10, 11, 21, and 22.

Claims 21-40 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement for the reasons stated on pages 2-3 of the Office Action. Applicants respectfully disagree.

As explained in the previous Amendment submitted on August 22, 2005, a number of examples in the application demonstrate treating or preventing inflammatory diseases or disorders, damage resulting from ischemia, injuries to the central nervous system and neurodegenerative disorders, pain, autoimmune diseases, cardiovascular disorders, or drug abuse, tolerance or dependence by administering a compound according to the invention. For example, Physiological Example 1 shows that the compounds are NMDA antagonists, which are known neuroprotectors in cases of, for example, acute insults (such as cerebral ischemia, stroke, hypoxia, anoxia, poisoning, hypoglycemia, mechanical trauma, and epilepsy) and chronic neurodegenerative states (such as Huntington's disease, Parkinson's disease, ALS, AIDS, and dementia). Physiological Examples 2 and 3 show anti-inflammatory and analgesic activities of the compounds *in vivo* and *in vitro*, as expressed by modulation of PGE_2, TNFα and NO (see Table 2), and Physiological Examples 4 to 7 show neuroprotective activities in cases of mechanical trauma (Example 4), stroke (Examples 5 and 6), and neurodegenerative disorders exemplified by Parkinson's disease (Example 7).

Physiological Example 9 shows cardioprotective activities, and Physiological Example 10 illustrates the ability of the compounds to prevent, and even reverse, tolerance to opioids.

Considering that a compound useful against a certain disease can be useful against other diseases sharing a common mechanism of action, Applicants respectfully submit that a person skilled in the art would understand the utility of the present compounds against diseases other than those specifically shown in the examples. Moreover, several illustrative mechanisms of action are identified in the application, which include blocking of excitatory amino acid receptor-mediated toxicity (e.g., NMDA receptor antagonism); antioxidative activity (e.g., by NOS inhibition); anti-inflammatory activity (e.g., by inhibition of prostaglandin); analgesic activity (e.g., NMDA antagonism and PGE_2 inhibition); and immunomodulatory activity (e.g., by inhibition of TNF-α) (see para. [0020]; Table 2). Such disclosure of mechanisms of action provides further support for enablement by suggesting uses of the present compounds for known effects.

In referring to the Rogawski article (*Trends in Pharmacol. Sci.* 14:325-331 (1993)), the Examiner states that the article "does not teach that NMDA receptor antagonism is an effective treatment of the disease state" and that "[j]ust because a compound acts at a receptor site does not mean the compound will be effective in treating disease/condition associated with that site" (Office Action, at p. 2). The Examiner further states that, because Rogawski relates to 2,3-benzodazepines, "compounds structurally removed from the claimed cannabinoid derivatives," a skilled artisan would lack motivation to extrapolate the results disclosed in Rogawski (*id.*).

However, many therapeutic targets of NMDA antagonists are known in the art. The reason that literature does not focus on a specific chemical class or structure is because of the insignificance of the chemical class or structure in understanding the pathways and therapeutic effects of NMDA antagonists. In fact, any molecule targeting the same pathway or receptor is expected to have a similar therapeutic effect, independent of its structure. For example, Stuart A. Lipton et al., "Mechanisms of Disease: Excitatory Amino Acids as a Final Common Pathway for Neurologic Disorders," *The New England Journal of Medicine*, vol. 330, no. 9, 613-22 (1994) lists neurologic disorders which are known to be modulated at least in part by NMDA antagonists (see Tables 1 and 2). A copy of this article is attached as Exhibit A.

With respect to the recitation of "preventing" in claim 21, Applicants respectfully submit that such "prevention" is demonstrated in the examples of this application in which the claimed compounds are administered before the injury as prophylactic agents. For example, Example 4 demonstrates the preventive effect of the tested compound by administering the compound 30 minutes before, and up to two hours after, head trauma, upon which edema formation and BBB disruption are significantly reduced (see para. [0266]). The specification further discloses the preventive effect of the claimed compound in preventing the undesirable, but commonly observed, development of tolerance to opioids when the patient is pretreated with the claimed compound (see para. [0424]). Thus, based on the disclosure in the specification, a person having ordinary skill in the art would be able to recognize medical conditions for which the claimed compounds are expected to provide preventive benefits.

In order to expedite prosecution of this application, however, independent claim 21 is amended to recite "alleviating" instead of "preventing." Support for this amendment is found in the specification, for example in paragraph [0021].

Accordingly, the rejections based on enablement, under 35 U.S.C. § 112, first paragraph, should be withdrawn.

Claims 21-40 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement for the reasons stated on page 3 of the Office Action.

Applicants respectfully disagree. Not only are the diseases and conditions recited in the claims disclosed in the specification (see, for example, paras. [0091] to [0103]), but a person having ordinary skill in the art is well aware of the disorders which can be treated with the compounds having the activities described in the specification.

For example, Adam Bisaga et al., "In search of a new pharmacological treatment for drug and alcohol addiction: N-methyl-D-aspartate (NMDA) antagonists," *Drug and Alcohol Dependence* 59:1-15 (2000), a copy of which is attached as Exhibit B, explains that NMDA antagonists can block a common pathway of action shared by addictive substances belonging to various chemical classes and structures. The following are listed as examples of addictive substances: alcohol, nicotine, opioids, morphine, heroin, cocaine, amphetamine, sedatives,

benzodiazepines, diazepam, and barbiturates. The article also describes animal models and clinical studies in which tolerance to or dependence on these substances was prevented or reverted by NMDA antagonists, and discloses the potential utility of NMDA receptor antagonists in treating substance abuse. Thus, this article shows that a person of ordinary skill in the art would clearly understand, from the description in the specification, the benefits of the present compounds in treating drug or substance abuse. Likewise, based on the disclosure of the activities of the presents compounds as well as specific diseases and conditions that can be treated with the compounds, and further in view of the knowledge in the art at the filing of this application, a skilled artisan would understand which and how certain conditions are intended to be treated or alleviated with the present compounds.

Therefore, Applicants respectfully submit that the disclosure in the specification complies with the written description requirement. Accordingly, all rejections under 35 U.S.C. § 112, first paragraph, should be withdrawn.

In addition, new claims 41-42 are added as being directed to embodiments of the invention. These claims recite administration of more specific examples of the compounds according to the invention for treating or alleviating activities or conditions specifically demonstrated in the physiological examples. Hence, the new claims are further supported by explicit examples and are further allowable for that reason.

In view of the above, the entire application is believed to be in condition for allowance, early notification of which would be appreciated. Should the Examiner not agree, a personal or telephonic interview is respectfully requested to discuss any remaining issues in order to expedite the eventual allowance of the claims.

Respectfully submitted,

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